PATENT
Docket No. 300622000501

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May 9, 2001 — Date

Karen LePari

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Chaitan KHOSLA, et al.

Serial No.: Not yet assigned

Filing Date: May 9, 2001

For: COMBINATORIAL POLYKETIDE LIBRARIES PRODUCED USING A MODULAR PKS GENE CLUSTER AS SCAFFOLD

Examiner: Not yet assigned

Group Art Unit: Not yet assigned

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to examination of the above-identified application, the Examiner is respectfully requested to enter the following amendments. Enclosed is the following Exhibit A:

Exhibit A: Marked-up Version of Amendments to the Specification and Claims.

AMENDMENTS

In the Specification:

Please replace the title of the above-identified application with the following:

--MACROLIDE ANALOG--

Please amend paragraph one of the specification as follows:

--This application is a continuation of copending U.S. Serial No. 09/073,538, filed 6 May 1998, which is a continuation-in-part of copending U.S. Serial No. 08/846,247, filed 30 April 1997, which is a continuation-in-part of U.S. Serial No. 08/486,645, filed 7 June 1995, now U.S. Patent No. 5,712,146, which is continuation-in-part of U.S. Serial No. 08/238,811, filed 6 May 1994, now U.S. Patent No. 5,672,491, which is a continuation-in-part of U.S. Serial No. 08/164,301, filed 8 December 1993, now abandoned, which is a continuation-in-part of U.S. Serial No. 08/123,732, filed 20 September 1993, now abandoned. Priority is claimed under 35 USC § 120. Priority is also claimed under 35 USC 119(e) with respect to U.S. Serial No. 60/076,919, filed 5 March 1998, now lapsed. The disclosures of these applications are incorporated herein by reference.

This application is also a continuation of copending U.S. Serial No. 09/311,756, filed 14 May 1999, which is a continuation of U.S. Serial No. 09/164,306, filed 1 October 1998, now abandoned, which claims benefit of priority to PCT Application No. PCT/US98/14911, filed 17 July 1998, which claims benefit of priority to U.S. Serial No. 08/896,323, filed 7 July 1997, now U.S. Patent No. 6,066,721, which is a continuation-in-part of U.S. Serial No. 08/675,817, filed 5 July 1996, now U.S. Patent No. 6,080,555, which claims benefit of priority under 35 USC 119(e) to U.S. Serial No. 60/003,338, filed 6 July 1995, now lapsed. The disclosures of these applications are incorporated herein by reference.--

In the Claims:

Please replace present claims 3-5 with the following claims 3-5:

3. (Amended) The method of claim 1 wherein said nucleotide sequence encodes at least three PKS modules.

4. (Amended) The method of claim 1 wherein said modifying results in utilization of a different extender unit; and/or

wherein said modifying results in utilization of a different starter unit; and/or

wherein said modification results in a polyketide of a different chain length.

5. (Amended) A nucleic acid comprising a nucleotide sequence encoding a modified PKS obtainable by the method of claim 1.

Please replace present claim 11 with the following claim 11:

11. (Amended) A method to construct a library of colonies containing expression vectors for a multiplicity of different polyketide synthases which method comprises transforming recombinant host cells with a mixture of expression vectors containing the nucleotide sequences obtained by the method of claim 1; and

separating the transformed cells into individual colonies, and culturing the colonies.

Please replace present claim 15 with the following claim 15:

15. (Amended) A method to produce a library of modular PKS proteins which method comprises culturing the multiplicity of cell colonies or the library of colonies of claim 13 under conditions wherein said expression vectors effect production of said modular PKS proteins.

Please replace present claim 19 with the following claim 19:

19. (Amended) A method to produce a combinatorial library of polyketides which method comprises culturing the cell colonies or library of colonies of claim 17 under conditions wherein polyketides whose synthesis is effected by said different PKS proteins are produced.

Please replace present claim 23 with the following claim 23:

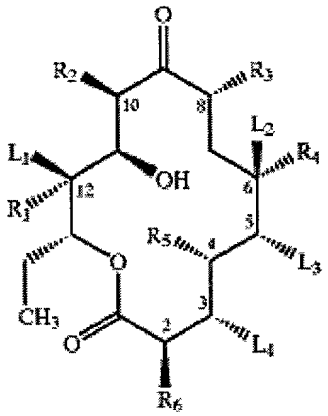
23. (Amended) A method to identify a successful candidate polyketide which binds to or reacts with a target moiety, which method comprises screening the library of claim 20 by

contacting each polyketide in said library with the target moiety under conditions wherein a successful candidate would form a complex with said target moiety, and

detecting any complex formed, thus identifying a polyketide of the library as the successful candidate.

Please add new claims 29 through 58 listed below.

29. (new) A compound of the formula:



wherein R_1, R_2, R_3, R_4, R_5, and R_6 are independently selected from Q wherein Q is selected from the group consisting of (a) --H, (b) --Me, (c) --Et, and (d) --OH;

L_1 and L_2 are independently --H or --OH;

L_3 is D-desosamine or --OH; and

L_4 is L-mycarose, L-cladinose or --OH

with the proviso that when R_1 -R_5 are --Me, R_6 is other than --H or --Me.

30. (new) The compound of claim 29 wherein Q is selected from the group consisting of (a), (b), and (c) and L_1, L_2, L_3 and L_4 are as defined therein.

31. (new) The compound of claim 29 wherein Q is selected from the group consisting of (a), (b), and (d) and L_1, L_2, L_3 and L_4 are as defined therein.

32. (new) The compound of claim 29 wherein Q is selected from the group consisting of (a), (c), and (d) and L_1, L_2, L_3 and L_4 are as defined therein.

33. (new) The compound of claim 29 wherein Q is selected from the group consisting of (b), (c), and (d) and L_1, L_2, L_3 and L_4 are as defined therein.

34. (new) The compound of claim 29 wherein Q is selected from the group consisting of (a) and (b) and L_1, L_2, L_3 and L_4 are as defined therein.

35. (new) The compound of claim 29 wherein Q is selected from the group consisting of (a) and (c) and L_1, L_2, L_3 and L_4 are as defined therein.

36. (new) The compound of claim 29 wherein Q is selected from the group consisting of (a) and (d) and L_1, L_2, L_3 and L_4 are as defined therein.

37. (new) The compound of claim 29 wherein Q is selected from the group consisting of (b) and (c) and L_1, L_2, L_3 and L_4 are as defined therein.

38. (new) The compound of claim 29 wherein Q is selected from the group consisting of (b) and (d) and L_1, L_2, L_3 and L_4 are as defined therein.

39. (new) The compound of claim 29 wherein Q is selected from the group consisting of (c) and (d) and L_1, L_2, L_3 and L_4 are as defined therein.

40. (new) The compound of claim 29 wherein Q is (a) and L_1, L_2, L_3 and L_4 are as defined therein.

41. (new) The compound of claim 29 wherein Q is (c) and L_1, L_2, L_3 and L_4 are as defined therein.

42. (new) The compound of claim 29 wherein Q is (d) and L_1, L_2, L_3 and L_4 are as defined therein.

43. (new) The compound of claim 29 wherein

(a) R_6 and R_1 are --H and R_2, R_3, R_4 and R_5 are --Me,

(b) R_5 and R_1 are --H and R_2, R_3, R_4 and R_6 are --Me,

(c) R_4 and R_1 are --H and R_2, R_3, R_5 and R_6 are --Me,

(d) R_3 and R_1 are --H and R_2, R_4, R_5 and R_6 are --Me,

(e) R_2 and R_1 are --H and R_3, R_4, R_5 and R_6 are --Me,

(f) R_6 and R_2 are --H and R_1, R_3, R_4 and R_5 are --Me,

(g) R_5 and R_2 are --H and R_1, R_3, R_4 and R_6 are --Me,

(h) R_4 and R_2 are --H and R_1, R_3, R_5 and R_6 are --Me,

(i) R_3 and R_2 are --H and R_1, R_4, R_5 and R_6 are --Me,

(j) R_6 and R_3 are --H and R_1, R_2, R_4 and R_5 are --Me,

(k) R_5 and R_3 are --H and R_1, R_2, R_4 and R_6 are --Me,

(l) R_4 and R_3 are --H and R_1, R_2, R_5 and R_6 are --Me,

(m) R_6 and R_4 are --H and R_1, R_2, R_3 and R_5 are --Me,

(n) R_5 and R_4 are --H and R_1, R_2, R_3 and R_6 are --Me,

(o) R_6 and R_5 are --H and R_1, R_2, R_3 and R_4 are --Me, and

L_1, L_2, L_3 and L_4 are as defined therein.

44. (new) The compound of claim 43 wherein (a)-(o) are as defined therein, L_1 and L_2 are --OH, L_3 is D-desosamine and L_4 is L-cladinose.

45. (new) The compound of claim 29 wherein

(a) R_6, R_2 and R_1 are --H and R_3, R_4 and R_5 are --Me,

(b) R_5, R_2 and R_1 are --H and R_3, R_4 and R_6 are --Me,

(c) R_4, R_2 and R_1 are --H and R_3, R_5 and R_6 are --Me,

(d) R_3, R_2 and R_1 are --H and R_4, R_5 and R_6 are --Me,

(e) R_6, R_3 and R_1 are --H and R_2, R_4 and R_5 are --Me,

(f) R_5, R_3 and R_1 are --H and R_2, R_4 and R_6 are --Me,

(g) R_4, R_3 and R_1 are --H and R_2, R_5 and R_6 are --Me,

(h) R_6, R_4 and R_1 are --H and R_2, R_3 and R_5 are --Me,

(i) R_5, R_4 and R_1 are --H and R_2, R_3 and R_6 are --Me,

(j) R_6, R_5 and R_1 are --H and R_2, R_3 and R_4 are --Me,

(k) R_6, R_3 and R_2 are --H and R_1, R_4 and R_5 are --Me,

(l) R_5, R_3 and R_2 are --H and R_1, R_4 and R_6 are --Me,

(m) R_4, R_3 and R_2 are --H and R_1, R_5 and R_6 are --Me,

(n) R_6, R_4 and R_2 are --H and R_1, R_3 and R_5 are --Me,

(o) R_5, R_4 and R_2 are --H and R_1, R_3 and R_6 are --Me,

(p) R_6, R_5 and R_2 are --H and R_1, R_3 and R_4 are --Me,

(q) R_6, R_4 and R_3 are --H and R_1, R_2 and R_5 are --Me,

(r) R_5, R_4 and R_3 are --H and R_1, R_2 and R_6 are --Me,

(s) R_6, R_5 and R_3 are --H and R_1, R_2 and R_4 are --Me, or

(t) R_6, R_5 and R_4 are --H and R_1, R_2 and R_3 are --Me, and

L_1, L_2, L_3 and L_4 are as defined therein.

46. (new) The compound of claim 45 wherein (a)-(t) are as defined therein, L_1 and L_2 are --OH, L_3 is D-desosamine and L_4 is L-cladinose.

47. (new) The compound of claim 29 wherein

(a) R_6, R_3, R_2 and R_1 are --H and R_5, and R_4 are --Me,

(b) R_5, R_3, R_2 and R_1 are --H and R_6, and R_4 are --Me,

(c) R_4, R_3, R_2 and R_1 are --H and R_5, and R_6 are --Me,

(d) R_6, R_4, R_2 and R_1 are --H and R_3, and R_5 are --Me,

(e) R_5, R_4, R_2 and R_1 are --H and R_3, and R_6 are --Me,

(f) R_6, R_5, R_2 and R_1 are --H and R_3, and R_4 are --Me,

(g) R_6, R_4, R_3 and R_1 are --H and R_2, and R_5 are --Me,

(h) R_5, R_4, R_3 and R_1 are --H and R_2, and R_6 are --Me,

(i) R_6, R_5, R_4 and R_1 are --H and R_2, and R_3 are --Me,

(j) R_2, R_4, R_3 and R_1 are --H and R_5, and R_6 are --Me,

(k) R_6, R_4, R_3 and R_2 are --H and R_1, and R_5 are --Me,

(l) R_5, R_4, R_3 and R_2 are --H and R_1, and R_6 are --Me,

(m) R_6, R_5, R_3 and R_2 are --H and R_1, and R_4 are --Me, or

(n) R_6, R_5, R_4 and R_3 are --H and R_1, and R_2 are --Me, and

L_1, L_2, L_3 and L_4 are as defined therein.

48. (new) The compound of claim 47 wherein (a)-(n) are as defined therein, L_1 and L_2 are --OH, L_3 is D-desosamine and L_4 is L-cladinose.

49. (new) The compound of claim 29 wherein

(a) R_5, R_4, R_3, R_2 and R_1 are --H and R_6 is --Me,

(b) R_6, R_4, R_3, R_2 and R_1 are --H and R_5 is --Me,

(c) R_6, R_5, R_3, R_2 and R_1 are --H and R_4 is --Me,

(d) R_6, R_5, R_4, R_2 and R_1 are --H and R_3 is --Me,

(e) R_6, R_5, R_4, R_3 and R_1 are --H and R_2 is --Me, or

(f) R_6, R_5, R_4, R_3 and R_2 are --H and R_1 is --Me, and

L_1, L_2, L_3 and L_4 are as defined therein.

50. (new) The compound of claim 49 wherein (a)-(f) are as defined therein, L_1 and L_2 are --OH, L_3 is D-desosamine and L_4 is L-cladinose.

51. (new) The compound of claim 29 wherein R_1, R_2, R_3, R_4, R_5 and R_6 are --H and L_1, L_2, L_3 and L_4 are as defined therein.

52. (new) The compound of claim 51 wherein R_1, R_2, R_3, R_4, R_5 and R_6 are as defined therein, L_1 and L_2 are --OH, L_3 is D-desosamine and L_4 is L-cladinose.

53. (new) The compound of claim 29 elected from the group consisting of 6,10-didesmethyl-6-ethylerythromycin A; 10,12-didesmethyl-12-deoxy-12-ethylerythromycin A; 10,12-didesmethyl-12-deoxy-10-hydroxyerythromycin A: 6,10,12-tridesmethyl-6,12-diethylerythromycin A, and 6,10,12-tridesmethyl-6-deoxy-6,12-diethylerythromycin A.

54. (new) The compound of claim 29 elected from the group consisting of 10-desmethylerythronolide B, 10-desmethyl-6-deoxyerythronolide B, 12-desmethylerythronolide B, 12-desmethyl-6-deoxyerythronolide B, 12-desmethyl-12-ethylerythronolide B, 6-desmethyl-6-deoxy-6-ethylerythronolide B, 10-desmethylerythromycin A, 10-desmethyl-12-deoxyerythromycin A, 10-desmethyl-6,12-dideoxyerythromycin A, 12-desmethylerythromycin A, 12-desmethyl-12-deoxyerythromycin A, 12-desmethyl-6,12-dideoxyerythromycin A, 6-

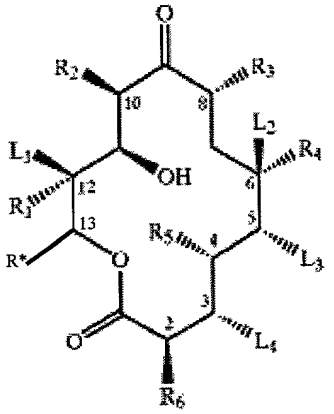
desmethyl-6-ethylerythromycin A, 12-desmethyl-12-ethylerythromycin A, 12-desmethyl-12-deoxy-12-ethylerythromycin A, 10-desmethyl-10-hydroxyerythromycin A, 12-desmethyl-12-epihydroxyerythromycin A, 10,12-didesmethylerythromycin A, 10,12-didesmethyl-12-deoxyerythromycin A, and 10,12-didesmethyl-6,12-dideoxyerythromycin A.

55. (new) The compound of claim 29 elected from the group consisting of 10-desmethylerythronolide B, 10-desmethyl-6-deoxyerythronolide B, 12-desmethylerythronolide B, 12-desmethyl-6-deoxyerythronolide B, 10-desmethylerythromycin A, 10-desmethyl-12-deoxyerythromycin A, 10-desmethyl-6,12-dideoxyerythromycin A, 12-desmethylerythromycin A, 12-desmethyl-12-deoxyerythromycin A, 12-desmethyl-6,12-dideoxyerythromycin A, 10,12-didesmethylerythromycin A, 10,12-didesmethyl-12-deoxyerythromycin A, and 10,12-didesmethyl-6,12-dideoxyerythromycin A.

56. (new) A compound selected from the group consisting of 10-desmethylerythromycin A, 10-desmethyl-12-deoxyerythromycin A, and 12-desmethyl-12-deoxyerythromycin A.

57. (new) The compound 6-desmethyl-6-ethylerythromycin A.

58. (new) A compound of the formula:



wherein R_1, R_2, R_3, R_4, R_5, and R_6 are independently selected from Q wherein Q is selected from the group consisting of (a) --H, (b) --Me, (c) --Et, and (d) --OH;

wherein R* is a straight chain, branched or cyclic, saturated or unsaturated substituted or unsubstituted hydrocarbyl of 1-15C;

L_1 and L_2 are independently --H or --OH;

L_3 is D-desosamine or --OH; and

L_4 is L-mycarose, L-cladinose or --OH

with the proviso that when R_1 -R_5 are --Me, R_6 is other than --H or --Me.

REMARKS

Claims 1 through 28 are now pending. Claims 3-5, 11, 15, 19 and 23 have been amended to remove multiple dependencies. Claims 29 through 58 have been added. Support therefor can be found, for example, at pages 21 and 22 of the specification. The title has been amended for clarification. The specification has been amended to provide additional priority information.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 300622000501. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: May 9, 2001 By: Brenda J. Wallach

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EXHIBIT A. VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

[COMBINATORIAL POLYKETIDE LIBRARIES PRODUCED USING A MODULAR PKS GENE CLUSTER AS SCAFFOLD] MACROLIDE ANALOGS

This application is a continuation of copending U.S. Serial No. 09/073,538 filed 6 May 1998 which is a continuation-in-part of U.S. Serial No. 08/846,247 filed 30 April 1997 which is a continuation-in-part of U.S. Serial No. 08/486,645 filed 7 June 1995 which is continuation-in-part of U.S. Serial No. 08/238,811 filed 6 May 1994 now U.S. Patent No. 5,672,491, which is a continuation-in-part of U.S. Serial No. 08/164,301 filed 8 December 1993, now abandoned, which is a continuation-in-part of U.S. Serial No. 08/123,732 filed 20 September 1993, now abandoned. Priority is claimed under 35 USC § 120. Priority is also claimed under 35 USC 119(e) with respect to U.S. [Provisional application] Serial No. 60/076,919 filed 5 March 1998, now lapsed. The disclosures of these applications are incorporated herein by reference.

In the Claims:

3. (Amended) The method of claim 1 [or 2] wherein said nucleotide sequence encodes at least three PKS modules.

4. (Amended) The method of [any of] claim[s] 1[-3] wherein said modifying results in utilization of a different extender unit; and/or

wherein said modifying results in utilization of a different starter unit; and/or

wherein said modification results in a polyketide of a different chain length.

5. (Amended) A nucleic acid comprising a nucleotide sequence encoding a modified PKS obtainable by the method of [any of] claim[s] 1[-4].

11. (Amended) A method to construct a library of colonies containing expression vectors for a multiplicity of different polyketide synthases which method comprises transforming

recombinant host cells with a mixture of expression vectors containing the nucleotide sequences obtained by the method of [any of] claim[s] 1[-4]; and

separating the transformed cells into individual colonies, and culturing the colonies.

15. (Amended) A method to produce a library of modular PKS proteins which method comprises culturing the multiplicity of cell colonies or the library of colonies of claim 13 [or 14] under conditions wherein said expression vectors effect production of said modular PKS proteins.

19. (Amended) A method to produce a combinatorial library of polyketides which method comprises culturing the cell colonies or library of colonies of claim 17 [or 18] under conditions wherein polyketides whose synthesis is effected by said different PKS proteins are produced.

23. (Amended) A method to identify a successful candidate polyketide which binds to or reacts with a target moiety, which method comprises screening the library of claim 20[, 21 or 22] by contacting each polyketide in said library with the target moiety under conditions wherein a successful candidate would form a complex with said target moiety, and

detecting any complex formed, thus identifying a polyketide of the library as the successful candidate.